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(54) Use of a farnesyl-protein transferase inhibitors for the manufacture of a medicament for blocking neoplastic transformation of cells induced by ras oncogenes.

(57) A method is provided by blocking or preventing the prenylation of CAAX box containing proteins including ras oncogene products thereby preventing and/or treating ras-related tumors which includes the step of administering a therapeutically effective amount of a protein-prenyl transferase inhibitor.

EP 0 537 007 A1

The present invention relates to a method for treating and/or prev nting tumors by blocking the pr nylation of CAAX box containing proteins, including ras oncog ne products, by administ ring a therapeutic amount of a protein-prenyl transferase inhibitor. Other aspects of th invention are set forth in the claims.

The products of ras genes comprise a family of guanine nucleotide binding proteins that are involved in the control of eukaryotic cell proliferation. Specific point mutations result in ras oncoproteins which have the ability to neoplasticly transform mammalian cells, and activated ras genes have been observed in at least 10% of all human tumors. Their incidence in certain malignancies, such as in colorectal and pancreatic cancers, is far greater.

Genetic studies first established that ras proteins, referred to as ras p21, must be formed by post-translational modification of a precursor protein with a defined carboxy-terminal structure, in order to ex rt their biological function. This structure, known as the CAAX box, is formed of a conserved cysteine residue located four amino acid-residues from the carboxy terminus, which in the case of ras is position 186 (except in the K-ras4B p21 protein, in which cysteine is located at position 185), followed by two aliphatic amino acids and any carboxy-terminal aminoacid residue. Mutations affecting the basic CAAX box structure of oncogenic ras p21 proteins completely abolish their transforming activity, presumably by impeding their interaction with the inner side of the plasma membrane. Such interaction requires a series of post-translational modificati ns within the CAAX box motif which include (a) farnesylation of the cys residue of the CAAX box; (b) cleavage of the three carboxy-terminal amino acid residues; and (c) methylation of the free carboxyl group generated in the resulting carboxy-terminal farnesyl-cysteine residue. The interaction of these farnesylated ras p21 proteins with cellular membranes in some cases is further strengthened by palmitoylation of neighboring upstream cysteine residues. See Hancock, et al, June 30, 1989, Cell 57:1167-1177; and Casey, et al, November 1989, Proc. Natl. Acad. Sci. U.S.A. 86:8323-8327.

Recent studies have suggested that the donor of the farnesyl residue present in ras p21 proteins is farnesyl pyrophosphate (FPP), a precursor also in the biosynthesis of cholesterol. The transfer of the farnesyl group from FPP, the donor molecule, to ras proteins is mediated by the enzyme, protein-farnesyl transferase (FT).

Treatment of S. cerevisiae cells or Xenopus oocytes with inhibitors of HMG-CoA reductase, the enzym responsible for the synthesis of mevalonic acid, the precursor of isoprenoid compounds, blocks the functi n of ras proteins in these cells. These results have raised the possibility of using inhibitors of cholesterol biosynthesis, that is, HMG CoA reductase inhibitors, to block neoplastic transformation induced by ras oncogen s. See, Schafer, et al, July 28, 1989, Science 245:379-385; and Goldstein and Brown, February 1, 1990, Nature 343:425-430.

Rine and Kim, "A Role for Isoprenoid Lipids in the Localization and Function of an Oncoprotein," The New Biologist, Vol. 2, No. 3 (March), 1990: pp 219-236, disclose at pages 222-223 that "lovastatin [also known as Mevacor], compactin, and related drugs that have been developed for the treatment of hypercholesterolemia act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the enzym that catalyzes the rate-limiting step in the synthesis of cholesterol and all other polyisoprenoids.... The drugs were tested in the Xenopus oocyte assay... for their ability to pharmacologically suppress activated H-Ras^{val12}.... These experiments pinpointed farnesyl pyrophosphate as the likely donor molecule for farnesylation of Ras protein, and suggested a rationale for a novel pharmacological route to block the action of this important human oncoprotein."

"Earlier work had already provided evidence that inhibition of isoprenoid synthesis by use of inhibitors of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase could slow the growth of tumors in animals. In particular, continuous, high levels of lovastatin caused substantial growth inhibition of a mouse neuroblastoma.... Although the oncogene(s) responsible for this tumor has not yet been identified and the dosage required to suppress the tumor was rather high, this study does support the notion that protein prenyl transferase(s) responsible for Ras modification might serve as useful targets for chemotherapy...."

European patent application No. 91107390.6, published as EP-A-456,180 on 13th November 1991, discloses protein-farnesyl transferase (FT) assays for identifying compounds that block the farnesylation of ras oncogene products. The Barbacid et al invention is based, in part, on the discovery and identification of the FT enzyme which catalyzes the transfer of the farnesyl group from the donor, farnesyl pyrophosphate (FPP), to the ras p21 Cys^{186} residue. Farnesylation of ras proteins is required for their attachment to the inner cell membrane and biological activity. Farnesylation of ras oncogene products is required for ras mediated transforming activity. Because the assays of the Barbacid et al invention are designed to target a step subsequ nt to th synthesis of FPP (in the cholesterol chain), th y allow for the identification f compounds that interfere with farnesylation of the ras oncog ne products and inhibit their transforming activity, yet do not interfere with the synthesis of FPP, a precursor in th synthesis of cholesterol, ubiquinones, dolichols and Haem A. Therefore, FT inhibitory compounds that d n t disrupt important cellular pathways which require FPP may be identified using the Barbacid t al assay.

Squalen synth tase is a microsomal enzyme which catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate (FPP) in the pres nce of nicotinamid adenine dinucleotid phosphat (reduced form) (NADPH) to form squal n (Poulter, C. D.; Rilling, H. C., in "Biosynthesis of Isoprenoid Compounds," Vol. I, Chapter 8, pp. 413-441, J. Wiley and S ns, 1981, and references therein). This enzyme is th first committed step of the de novo cholesterol biosynthetic pathway.

Squalene synthetase inhibitors which block the action of squalene synthetase (after the formation of farnesyl pyrophosphate) are disclosed in U.S. Patent Nos. 4,871,721 and 5,025,003, European patent applicati n No. 89115400.7 (EP-A-356,866), European patent application No. 90113700.0 (EP-A-409,181), and European patent application No. 92108074.3.

Preferred aspects of the invention will now be described.

In accordance with the present invention, it has been found that post-translational modification of CAAX box containing proteins may be inhibited by administering a protein-prenyl transferase inhibitor which inhibits the transfer of the prenyl group [such as farnesyl (in the case of ras oncogene products), geranyl or geranylgeranyl] to the cysteine of-the CAAX box by the protein-prenyl transferase enzyme. The protein-prenyl transferase inhibitor will block the protein-prenyl transferase enzyme from catalyzing the transfer of the prenyl group (for example, farnesyl, geranyl or geranylgeranyl) from the prenyl pyrophosphate to the cys residue of th CAAX box, such as the ras p21 cys, or to the CAAX box cysteine of other CAAX box containing proteins. In the case of ras p21 oncogene products, inasmuch as the cys will not be farnesylated it cannot effect interacti n of the ras protein with the membrane so that neoplastic transformation of the cell will be prevented. In this manner protein-prenyl transferase inhibitors prevent neoplastic transformation of the cell, thereby acting as an anti-cancer agent for the treatment of and/or prevention of ras-related tumors.

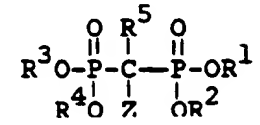
Examples of CAAX box containing proteins which have been demonstrated or are believed to underg prenylation include, but are not limited to, nuclear lamins, α or γ subunits of heterotrimeric G-proteins, γ-subunits of retinal transducin, G25K and k-rev p21, and protein families including rho, rap, rac, ral, and rab.

Thus, the present invention resides in a method for blocking or preventing the prenylation of CAAX box containing proteins such as ras oncogene products, and thereby inhibit disease promoting effects of the CAAX box containing protein or more specifically prevent and/or treat ras-related tumors, by administering to a patient in need of treatment a therapeutic amount of a protein-prenyl transferase inhibitor.

The protein-prenyl transferase inhibitors, unlike HMG CoA reductase inhibitors, will interfere with pr nylation of the ras oncogene products and inhibit their transforming activity, yet may or may not interfere with the synthesis of FPP, a precursor in the synthesis of ubiquinones, dolichols and Haem A.

The activity of the protein-prenyl transferase inhibitors in blocking the protein-prenyl (e.g. farnesyl, geranyl or geranylgeranyl) transferase from catalyzing the transfer of the prenyl group (e.g. farnesyl, geranyl or geranylgeranyl) from the prenyl pyrophosphate to the cys residue of the CAAX box may be assayed by the procedure described in U.S. application Serial No. 520,570 filed May 8, 1990, by Barbacid et al, the disclosure of which is incorporated herein by reference.

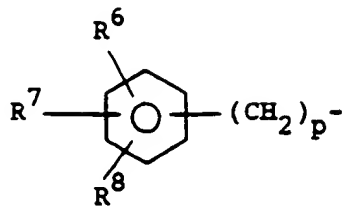
Protein-prenyl transferase inhibitors suitable for use herein include compounds disclosed in European patent application No. 92108074.3. These protein-prenyl transferase inhibitors have the following structure

I 

wherein R^1, R^2, R^3 and R^4 are the same or different and are H, alkyl, a metal ion or a prodrug ester;

R^5 is H, halogen or lower alkyl;

Z a lipophilic group containing at least 6 carbons and can be substituted alkenyl wherein the alkenyl group contains from 7 to 25 carbon atoms in the chain and from 1 to 4 double bonds; substituted alkynyl containing 1 to 4 triple bonds; mixed alkenyl-alkynyl containing 1 to 3 double bonds and 1 to 3 triple bonds and wherein alkenyl and/or alkynyl may be substituted or unsubstituted; or a substituted phenylalkyl group of the structure

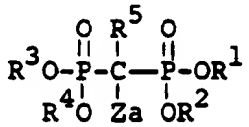


wherein $(CH_2)_p$ contains from 1 to 15 carbons, preferably 2 to 12 carbons, in the chain and may include 0, 1, 2 or 3 double bonds and/or 0, 1, 2 or 3 triple bonds in the normal chain, and/or may include 0, 1, 2 or 3 substituents; and R^6, R^7 and R^8 are the same or different and are H, alkyl containing 1 to 40 carbons, preferably from 3 to 15 carbons, alkoxy containing 1 to 40 carbons, preferably from 3 to 15 carbons, alkenyl containing 2 to 40 carbons, preferably from 3 to 15 carbons, alkenyloxy containing 2 to 40 carbons, preferably from 3 to 15 carbons, alkynyl containing 2 to 40 carbons, preferably from 3 to 15 carbons, alkynyloxy containing 2 to 40 carbons, preferably from 3 to 15 carbons, aryloxy, hydroxy, halogen, nitro, amino, thiol, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy,arylcarbonylamino or alkylcarbonylamino, at least one of R^6, R^7 and R^8 being alkenyl, alkenyl xy, alkynyl or alkynyloxy; and wherein the total number of carbons in the substituted phenylalkyl group exceeds 10 carbons.

The terms "substituted alkenyl" and "substituted alkynyl" as employed herein with respect to Z refers to alkenyl or alkynyl substituted with 1 to 4 groups which may be alkyl, alkenyl, alkynyl, halogen, hydroxy, alkoxy, alkenyloxy, alkynyloxy, aryl and/or cycloalkyl.

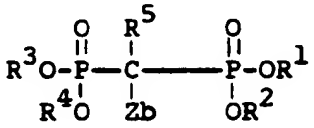
The $(CH_2)_p$ group may contain one or more alkyl, alkoxy, alkenyl, alkynyl, hydroxy and/or halogen substituents.

Preferred embodiments of formula I protein-prenyl transferase inhibitors have the structure

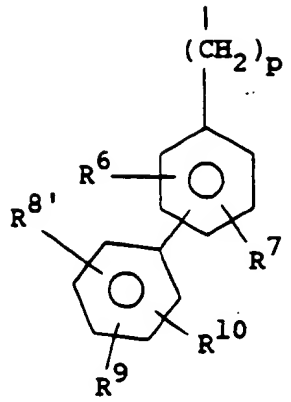
II 

wherein R^1, R^2, R^3, R^4 and R^5 are as defined above and Za is substituted alkenyl which includes from 1 t 4 double bonds and is substituted with from 1 to 4 alkyl groups.

In addition, other protein-prenyl transferase inhibitors suitable for use herein and disclosed in application No. 92108074.3 have the structure

III 

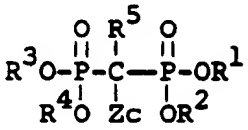
wherein
Zb is



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and $(CH_2)_p$ are as defined hereinbefore, except that R^6 and R^7 may b any one of the groups included under the definition R^6 and R^7, set out hereinbefore, without limitation; R^8, R^9 and R^{10} are the same or different and are as defined hereinbefore with respect to R^6 and R^7, without limitati n.

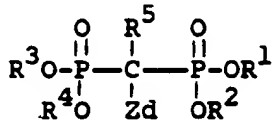
Preferred are compounds of formula III wherein the R^8, R^9, R^{10}-substituted phenyl is para to the R^6, R^7-phenylene. These compounds have been found to inhibit cholesterol biosynthesis when administered orally.

In another embodiment of the present invention, compounds which are protein-prenyl transferase inhibitors (disclosed in application No. 92108074.3) may be employed which have the structure

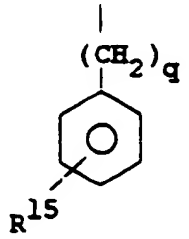
IV 

wherein R^1, R^2, R^3, R^4 and R^5 are as defined hereinbefore and Zc is alkyl wherein the alkyl group contains from 9 to 14 carbons in the normal chain and is substituted with 1, 2, 3 or 4 alkyl groups.

Still another embodiment of compounds which are protein-prenyl transferase inhibitors (disclosed in application No. 92108074.3) have the structure

V 

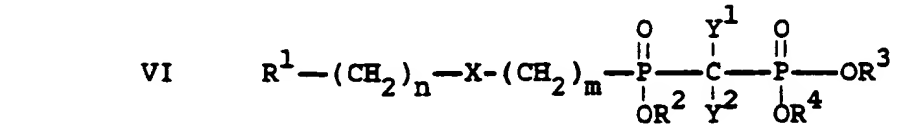
wherein
Zd is



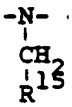
wherein R^1, R^2, R^3, R^4 and R^5 are as defined her inbefore and $(CH_2)_q$ contains at least 2 carbons in the chain and may include 0, 1, 2 or 3 double b nds and/or 0, 1, 2 or 3 triple bonds in the normal chain, preferably 3 to 7 carbons in the normal chain, and may include ne or more alkyl, alkenyl, alkynyl, alkoxy, hydroxy and/ r ha-

logen substituents; and R^{15} is alkyl containing from 2 to 20 carbons, and preferably is in the para position, and the total number of carbons in Zd exceeds 10.

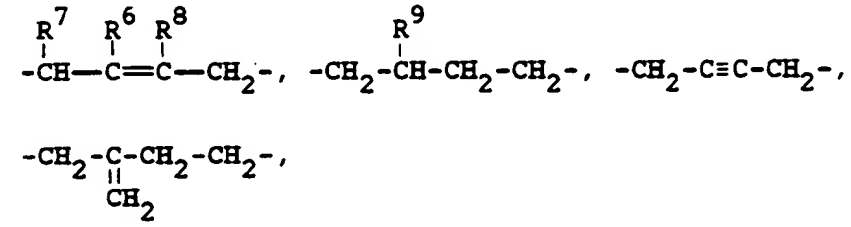
Other protein-prenyl transferase inhibitors suitable for use herein are compounds disclosed in EP-A-356,866 and EP-A-409,181, and have the following structure

VI 

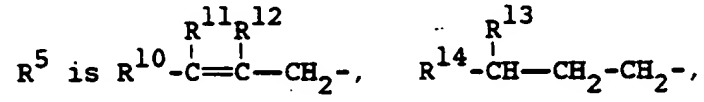
wherein m is 0, 1, 2 or 3; n is 0, 1, 2, 3 or 4; Y^1 and Y^2 are H or halogen, preferably H or F; R^2, R^3 and R^4 are independently H, metal ion, C_1 to C_8 alkyl or C_3 to C_2 alkenyl; X is O, NH,



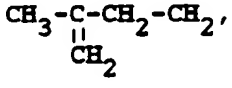
or S (wherein R^{15} is H or C_1 to C_5 alkyl); R^1 is R^5-Q^1-Q^2-Q^3-wherein Q^1, Q^2 and Q^3 are independently:



or a bond, with the stipulation that if Q^1 is a bond, then Q^2 and Q^3 must be bonds, and if Q^2 is a bond, then Q^3 is a bond; R^6 is H, lower alkyl, halo or haloalkyl (e.g. CH_2F, CF_3); R^7 is H, halogen, lower alkyl or alkylthi ; R^8 is H, halogen, trimethylsilyl or lower alkyl; R^9 is H, or lower alkyl;

R^5 is 

R^{16}-C≡C-CH_2-(wherein R^{16} is lower alkyl or H),



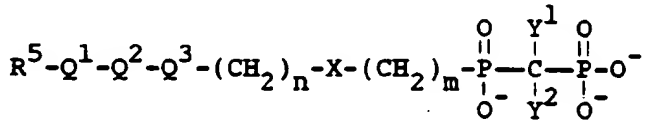
or $CH_3(CH_2)_p$- where p is 2 to 7; R^{10} and R^{11} are independently hydrogen, lower alkyl such as methyl or ethyl, halogen, lower alkenyl or haloalkyl or R^{10} and R^{11} can be taken together to form $(CH_2)_s$, where s is 2 to 7; R^{12} is hydrogen, lower alkyl, halog n or lower alkenyl; R^{13} and R^{14} are independently lower alkyl such as methyl or ethyl; with the provisos that if all f Q^1, Q^2 and Q^3 are bonds, then R^{10} and R^{11} cannot both be H, and R^6 cannot b $CH_3(CH_2)_p$-, with $p \leq 4$; if m is , X is other than S; and if m is o and X is 0, then n is 1, 2, 3 or 4, including all stereoisomers thereof.

Th term "lower alkenyl" or "alkenyl" as used above by itself or as part of another group refers to straight

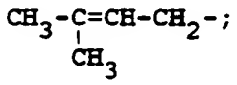
or branched chain radicals of 2 to 12 carbons, preferably 3 to 6 carbons in the normal chain, which includ one d uble bond in th normal chain, and which may include an aryl r alkyl substituent, such as vinyl, 2-propenyl, 2-butenyl, 3-phenyl-2-propenyl, 2-pentenyl, 2-h x nyl, 2-h ptenyl, 2-octenyl, 2-n nenyl, 2-decenyl, 2-undecenyl, 2-dodecenyl and the lik .

Preferred are those compounds of formula VI which have the following formula:

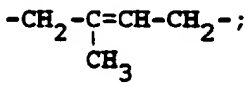
VII



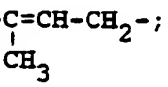
wherein R^5 is



Q^3 is a bond;
Q^2 is



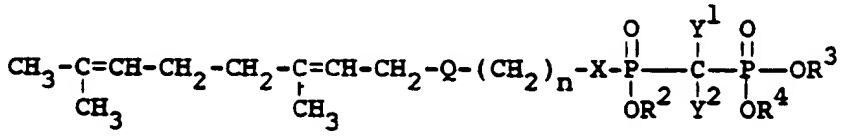
$-CH_2-C\equiv C-CH_2-$; or $-CH_2-CH=CH-CH_2-$;

Q^1 is 

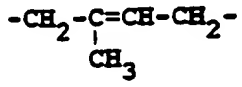
n is 0 or 1; m is 1 or 2; X is 0 and Y^1 and Y^2 are each H or F, in the form of the salts or acid.

In addition, preferred are those compounds of formula VI which have the following structure

VIA-A

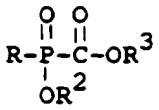


wherein Q is



or a bond; n is 1 or 2; X is 0, Y^1 and Y^2 are each H or each F; R^2, R^3 and R^4 are alkyl, H or m tal ions; or X is NH and n is 0.

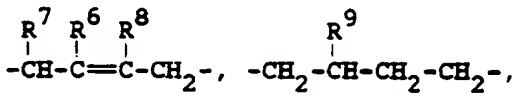
In addition, protein-prenyl transf rase inhibitors which may be employed herein includ compounds disclosed in U.S. Patent No. 5,025,003 to Biller and have the following structure

VIII 

wherein R^2 is a metal ion, lower alkyl or H;

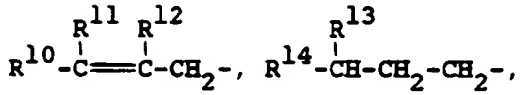
R^3 is a metal ion or lower alkyl;

R is R^1-$(CH_2)_n$-, R^1-$(CH_2)_m$O- or R^1-$(CH_2)_m$OCH_2-, wherein n is 1 to 4, m is 0 to 3; and R^1 is R^5-Q^1-Q^2-Q^3- wherein Q^1, Q^2 and Q^3 are independently:



$-CH_2-C\equiv C-CH_2-$, or a bond, with the stipulation that if Q^1 is a bond, then Q^2 and Q^3 must be bonds, and if Q^2 is a bond, then Q^3 is a bond; R^6 is H, lower alkyl, fluoro or fluoroalkyl (e.g., CH_2F, CF_3); R^7 is H, fluoro, low r alkyl or alkylthio; R^8 is H, fluoro, trimethylsilyl or lower alkyl; R^9 is H, or lower alkyl;

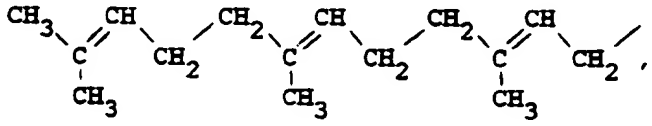
R^5 is



R^{16}-C≡C-CH_2- (wherein R^{16} is lower alkyl or H), or $CH_3(CH_2)_p$- where p is 2 to 7; R^{10} and R^{11} are independently hydrogen, lower alkyl such as methyl or ethyl, fluoro, lower alkenyl or fluoroalkyl or R^{10} and R^{11} can be taken together to form $(CH_2)_s$, where s is 2 to 7; R^{12} is hydrogen, lower alkyl, fluoro or lower alkenyl; R^{13} and R^{14} are independently lower alkyl such as methyl or ethyl; with the proviso that if all of Q^1, Q^2 and Q^3 are bonds, then R^{10} and R^{11} cannot both be H, and R^5 cannot be $CH_3(CH_2)_p$-, with p<4, including all stereoisomers thereof.

The term "lower alkenyl" or "alkenyl" as used herein is defined hereinbefore.

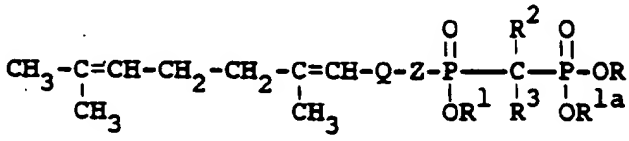
Preferred are those compounds of formula VIII wherein R^1 is



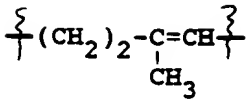
n is 1, 2 or 3, m is 1 or 2, R^2 is H or a metal ion, and R^3 is lower alkyl, a metal ion or H.

Other protein-prenyl transferase inhibitors suitable for use herein include compounds disclosed in U.S. Patent No. 4,871,721 to Biller and have the following structure:

IX



wherein Q is



or a bond;

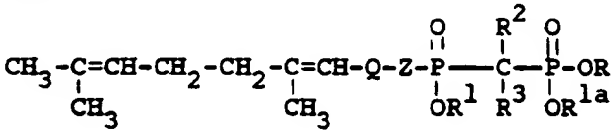
Z is $-(CH_2)_n-$ or $-(CH_2)_p-CH=CH-(CH_2)_m-$, wherein n is 1 to 5; p is 0, 1 or 2; m is 0, 1 or 2;

R, R^1 and R^{1a} may be the same or different and are H, lower alkyl or a metal ion; and

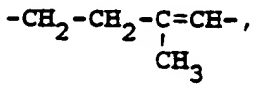
R^2 and R^3 may be the same or different and are H or halogen.

Preferred are those compounds of formula IX which have the following structure

IXA



wherein Q is



Z is $-CH_2CH_2-$ or -CH=CH-; R^2 and R^3 are each H or each F; R, R^1 and R^{1a} are OH or metal ions.

The disclosures of the above U.S. patents and U.S. patent applications are incorporated herein by reference.

In carrying out the method of the invention, a pharmaceutical composition will be employed containing at least one protein-prenyl transferase inhibitor in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can b administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or-powders, or they can be administered by a parenteral route in the f rm of injectable preparations. The dose for adults is preferably between 200 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

A typical capsule for oral administration contains protein-prenyl transferase inhibitor (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a N . 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 250 mg of sterile protein-prenyl transferase inhibitor into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

Claims

1. Use of a protein-prenyl transferase inhibitor for the manufacture of a medicament for treating and/or preventing ras-related tumors in a mammalian species.

2. Use of a protein-prenyl transferase inhibitor for the manufacture of a medicament for blocking the farnesylation of ras oncogene products in a mammalian species.

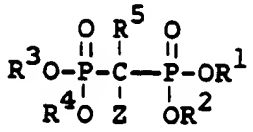
3. Use of a protein-prenyl transferase inhibitor for the manufacture of a medicament for blocking neoplastic transformation induced by ras oncogenes in a mammalian species.

4. Use of a protein-prenyl transferase inhibitor for th manufacture of a medicament for preventing pr nylation of the cys residue of the CAAX box of a ras protein to prevent ras oncogene activity in a mammalian

species.

5. Th us as defined in any of Claims 1, 2, 3 or 4 wherein the protein-prenyl transferase inhibitor is a bisphosph nate.

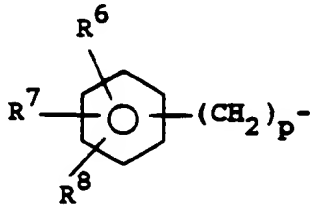
6. The method as defined in any of Claims 1, 2, 3 or 4 wherein the protein-prenyl transferase inhibitor has the structure

(a) 

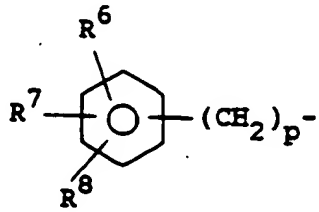
wherein R^1, R^2, R^3 and R^4 are the same or different and are H, lower alkyl, a metal ion or a prodrug ester;

R^5 is H, halogen or lower alkyl;

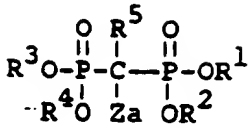
Z is substituted alkenyl wherein the alkenyl group contains at least 7 carbon atoms in the chain and from 1 to 4 double bonds; substituted alkynyl containing 1 to 4 triple bonds; mixed alkenyl-alkynyl containing 1 to 3 double bonds and 1 to 3 triple bonds, and wherein alkenyl and/or alkynyl may be substituted or unsubstituted; or a substituted phenylalkyl group of the structure



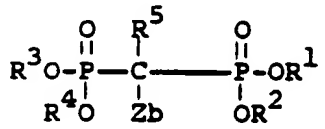
wherein $(CH_2)_p$ contains from 1 to 15 carbons in the chain and may include 0, 1, 2 or 3 double bonds and/or 0, 1, 2 or 3 triple bonds in the normal chain and/or may include 0, 1, 2 or 3 substituents which are alkyl, alkenyl, alkoxy, alkynyl, hydroxy and/or halogen; and R^6, R^7 and R^8 are the same or different and are H, alkyl containing 1 to 40 carbons, alkoxy containing 1 to 40 carbons, alkenyl containing 2 to 40 carbons, alkenyloxy containing 2 to 40 carbons, alkynyl containing 2 to 40 carbons, alkynyloxy, aryloxy, hydroxy, halogen, nitro, amino, thiol, alkylthio, arylthio, arylsulfinyl, alkylsulfinyl, arylsulfonyl, alkylsulfonyl, carboxy, alkoxycarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aminocarbonyl, arylcarbonylamino or alkylcarbonylamino, at least one of R^6, R^7 and R^8 being alkenyl, alkenyloxy, alkynyl or alkynyloxy, and wherein the total number of carbons in



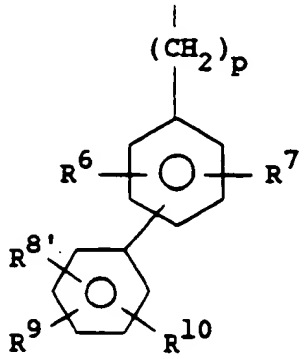
exceeds 10 carbons;

(b) 

wherein R^1, R^2, R^3 and R^4 are the same or different and are H, alkyl, a metal ion or a prodrug ester; R^5 is H, halogen or alkyl, and Za is substituted alkenyl which includes 1 to 4 double bonds and is substituted with from 1 to 4 lower alkyl groups;

(c) 

wherein Zb is



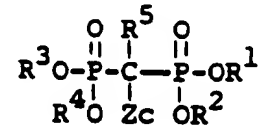
R^1, R^2, R^3 and R^4 are the same or different and are H, alkyl, a metal ion or a prodrug ester;

R^5 is H, halogen or alkyl;

p is 1 to 15;

$(CH_2)_p$ may include 0, 1, 2 or 3 double bonds and/or 0, 1, 2 or 3 triple bonds in the normal chain, and/or may include 0, 1, 2 or 3 substituents which are alkyl, alkoxy, alkenyl, alkynyl, hydroxy and/or halogen; and

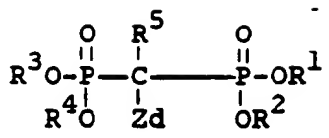
R^6, R^7, $R^{8'}$, R^9 and R^{10} are the same or different and are H, alkyl containing 1 to 40 carbons, alk xy containing 1 to 40 carbons, alkenyl containing 2 to 40 carbons, alkenyloxy containing 2 to 40 carbons, hydroxy, alkynyl containing 2 to 40 carbons, alkynyloxy containing 2 to 40 carbons, aryloxy, halogen, nitro, amino, thio, alkylthio, arylthio, arylsulfinyl, alkylsulfinyl, arylsulfonyl, alkylsulfonyl, carboxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyl, aminocarbonyl, arylcarbonylamino or alkylcarbonylamino;

(d) 

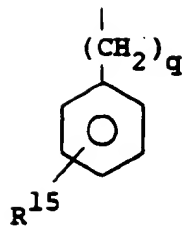
wherein Zc is substituted alkyl containing from 9 to 14 carbons in the normal chain and is substituted with 1 to 4 lower alkyl groups;

R^1, R^2, R^3 and R^4 are the sam or different and are H, alkyl, a metal ion or a prodrug ester; and

R^5 is H, halog n or alkyl;

(e) 

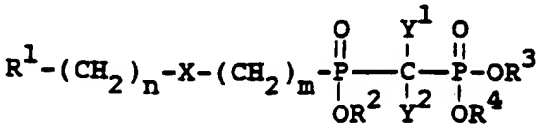
Wherein Zd is



q is 2 to 15, $(CH_2)_q$ may include 0, 1, 2 or 3 double bonds and/or 0, 1, 2 or 3 triple bonds in the normal chain and may optionally include one or more alkyl, alkenyl, alkynyl, hydroxy, alkoxy and/or halogen substituents;

R^1, R^2, R^3 and R^4 are the same or different and are H, alkyl, a metal ion or a prodrug ester; and R^5 is H, halogen or lower alkyl; and R^{15} is alkyl containing from 2 to 20 carbons;

the total number of carbons in Zd exceeds 10;

(f) 

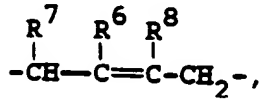
wherein m is 0, 1, 2 or 3; n is 0, 1, 2, 3 or 4;

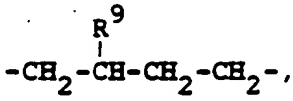
Y^1 and Y^2 are H or halogen;

R^2, R^3 and R^4 may be the same or different and are independently H, metal ion, C_1 to C_8 alkyl or C_3 to C_{12} alkenyl;

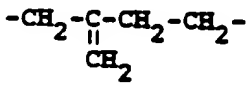
X is O, S, NH or $-NCH_2R^{15}$ wherein R^{15} is H or C_1 to C_5 alkyl; and

R^1 is R^5-Q^1-Q^2-Q^3- wherein Q^1, Q^2 and Q^3 are the same or different and are independently



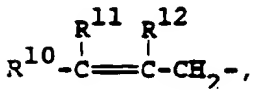


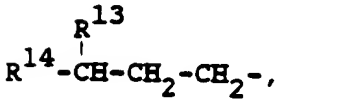
$-CH_2-C\equiv C-CH_2-$,

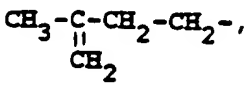


r a singl bond, with the proviso that if Q^1 is a b nd, then Q^2 and Q^3 are bonds, and if Q^2 is a bond th n Q^3 is a bond, and wherein R^6 is H, lower alkyl, hal or haloalkyl; R^7 is H, halogen, lower alkyl or lower alkylthio; R^8 is H, halogen, trimethylsilyl or l wer alkyl; and R^9 is H or lower alkyl;

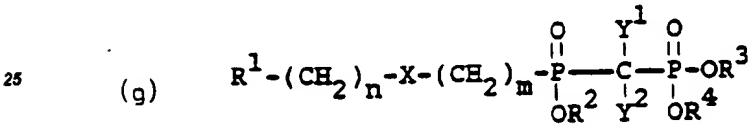
R^5 is







$CH_3(CH_2)_p$ where p is an integer from 2 to 7, or R^{16}-C≡C-CH_2- where R^{16} is H or lower alkyl; R^{10}, R^{11} are the same or different and are independently H, lower alkyl, haloalkyl, halogen or lower alkenyl or R^{10} and R^{11} can be taken together to form $(CH_2)_s$ where s is an integer from 2 to 7; R^{12} is H, lower alkyl, halog n or lower alkenyl; and R^{13} and R^{14} are the same or different and are independently lower alkyl; with th proviso that if all of Q^1, Q^2 and Q^3 are bonds, then R^{10} and R^{11} cannot both be H, and R^5 cann t b $CH_3(CH_2)_p$- with p less than or equal to 4, and when m is O, X is other than S; and if m is o and X is O, then n is 1, 2, 3 or 4; and including all stereoisomers- thereof ;

(g) 

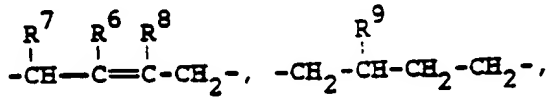
wherein m is 1, 2 or 3; n is 0, 1, 2, 3 or 4;

Y^1 and Y^2 are H or halogen;

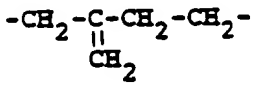
R^2, R^3 and R^4 may be the same or different and are independently H, metal ion, C_1 to C_8 alkyl or C_3 to C_{12} alkenyl;

X is O, S, NH or -NCH_2R^{15} wherein R^{15} is H or C_1 to C_5 alkyl; and

R^1 is R^5-Q^1-Q^2-Q^3- wherein Q^1, Q^2 and Q^3 are the same or different and are independently

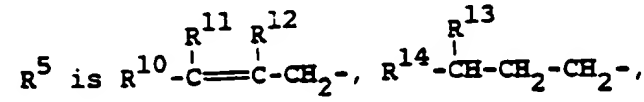


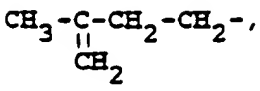
-CH_2-C≡C-CH_2-,



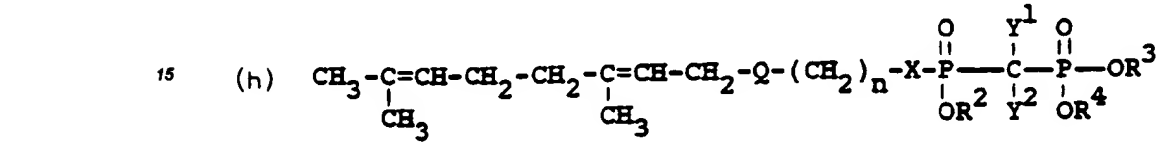
or a single bond, with the proviso that if Q^1 is a bond, then Q^2 and Q^3 are bonds, and if Q^2 is a bond then Q^3 is a bond, and wherein R^6 is H, lower alkyl, halo or haloalkyl; R^7 is H, halogen, lower alkyl, or lower alkylthio; R^8 is H, halogen, trimethylsilyl or lower alkyl; and R^9 is H or lower alkyl;

R^5 is

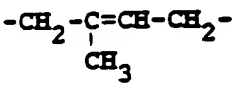




$CH_3(CH_2)_p$ where p is an integer from 2 to 7, or R^{16}-C≡C-CH_2- where R^{16} is H of lower alkyl; R^{10}, and R^{11} are the same or different and are independently H, lower alkyl, haloalkyl, halogen or lower alkenyl or R^{10} and R^{11} can be taken together to form $(CH_2)_s$ where s is an integer from 2 to 7; R^{12} is H, lower alkyl, halog n or lower alkenyl; and R^{13} and R^{14} are the same or different and are independently lower alkyl; with th proviso that if all of Q^1, Q^2 and Q^3 are bonds, then both R^{10} and R^{11} cannot be H, and R^5 cann t be $CH_3(CH_2)_p$- with a p less than or equal to 4, and including all stereo-isomers thereof ;

(h) 

wherein Q is



or a bond;

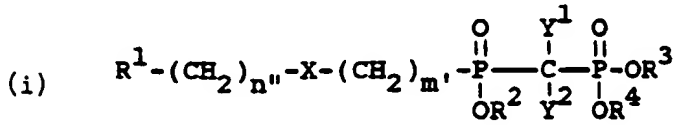
n is 0 to 4;

X is O, -NH- or NCH_2R^{15};

R^2, R^3 and R^4 are the same or different and are H, lower alkyl, lower alkenyl, or a metal ion; Y^1 and Y^2 may be the same or different and are H or halogen; and

R^{15} is H or lower alkyl;

with the proviso that when X is O, n is 1, 2, 3, or 4;

(i) 

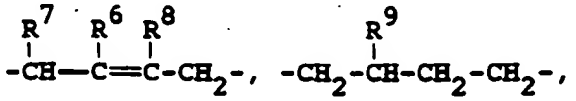
wherein m' is 1, 2 or 3; n" is 0, 1, 2 or 3;

Y^1 and Y^2 are H or halogen;

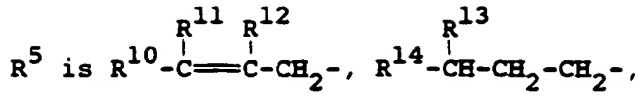
R^2, R^3 and R^4 may be the same or different and are independently H, metal ion, C_1 to C_8 alkyl or C_3 to C_{12} alkenyl;

X is O, S, NH or -NCO_2R^{15} wherein R^{15} is H or C_1 to C_6 alkyl; and

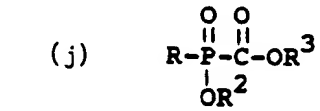
R^1 is R^5-Q^1-Q^2-Q^3- wherein Q^1, Q^2 and Q^3 are the same or different and are independently



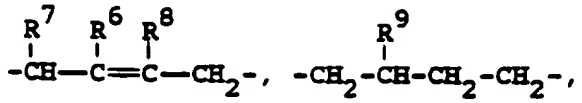
-CH2-C≡C-CH_2-, or a single b nd, with the proviso that if Q^1 is a bond, then Q^2 and Q^3 are bonds, and if Q^2 is a bond then Q^3 is a bond, and wherein R^6 is O, lower alkyl, hal or haloalkyl; R^7 is H, halogen, low r alkyl or lower alkylthi ; R^8 is H, halogen, trimethylsilyl or lower alkyl; and R^9 is H or lower alkyl;



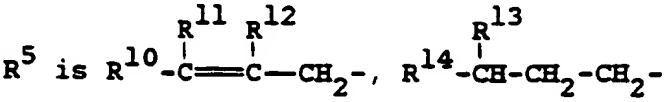
$CH_3(CH_2)_p$ where p is an integer from 2 to 7, or R^{16}-C≡C-CH_2- where R^{16} is H or lower alkyl; R^{10}, and R^{11} are the same or different and are independently H, lower alkyl, haloalkyl, halogen or lower alkenyl or R^{10} and R^{11} can be taken together to form $(CH_2)_s$ where s is an integer from 2 to 7; R^{12} is H, lower alkyl, halogen or lower alkenyl; and R^{13} and R^{14} are the same or different and are independently lower alkyl; with the proviso that if all of Q^1, Q^2 and Q^3 are bonds, then both R^{10} and R^{11} cannot be H, and R^5 cannot b $CH_3(CH_2)_p$- with a p less than or equal to 4, and including all stereoisomers thereof;



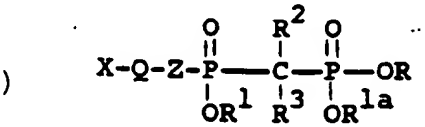
wherein R^2 is a metal ion, lower alkyl or H; R^3 is a metal ion or lower alkyl; R is R^1-$(CH_2)_n$-, R^1-$(CH_2)_m$O- or R^1-$(CH_2)_m$OCH_2-, wherein n is an integer from 1 to 4 and m is an integer from 0 to 3; and R^1 is R^5-Q^1-Q^2-Q^3- wherein Q^1, Q^2 and Q^3 are independently:



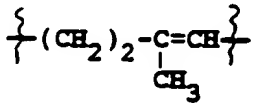
-CH_2-C≡C-CH_2-, or a bond, with the stipulation that if Q^1 is a bond, then Q^2 and Q^3 must be bonds, and if Q^2 is a bond, then Q^3 is a bond; R^6 is H, lower alkyl, fluoro or fluoroalkyl; R^7 is H, fluoro, lower alkyl or alkylthio; R^8 is H, fluoro, trimethylsilyl or lower alkyl; R^9 is H, or lower alkyl;



R^{16}-C≡C-CH_2- (wherein R^{16} is lower alkyl or H), or $CH_3(CH_2)_p$- where p is 2 to 7; R^{10} and R^{11} are independently hydrogen, lower alkyl, fluoro, lower alkenyl or fluoroalkyl or R^{10} and R^{11} can be taken together to form $(CH_2)_s$, where s is 2 to,7; R^{12} is hydrogen, lower alkyl, fluoro or lower alkenyl; R^{13} and R^{14} are independently lower alkyl; with the proviso that if all of Q^1, Q^2 and Q^3 are bonds, then R^{10} and R^{11} cannot both be H, and R^5 cannot be $CH_3(CH_2)_p$, with p ≤ 4, including all stereoisomers thereof;



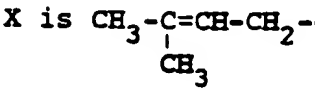
wherein Q is



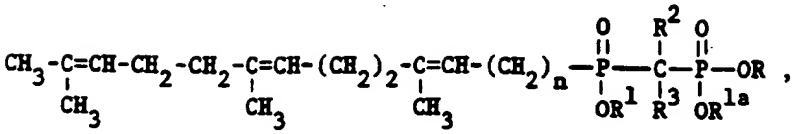
or a bond;

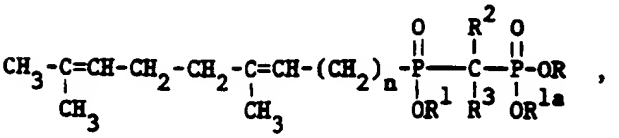
Z is -$(CH_2)_n$- or -$(CH_2)_p$-CH=CH-$(CH_2)_m$-, wherein n is 1 to 5; p is 0, 1 or 2; m is 0, 1 or 2;

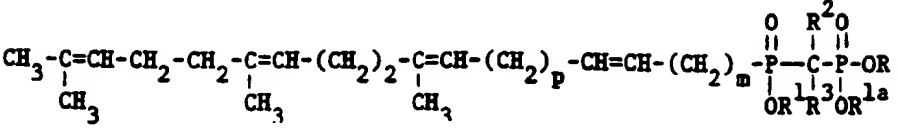
R, R^1 and R^{1a} are the same r different and are H, lower alkyl or a metal ion;
R^2 and R^3 may be the same or different and ar H or halogen; and

X is 

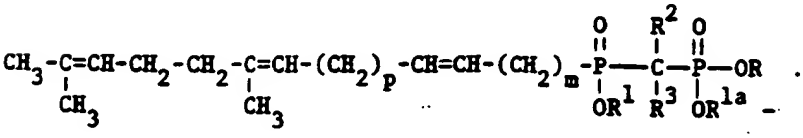
or

(1) 





or



7. Use of a protein-prenyl transferase inhibitor for the manufacture of a medicament for treating and/or preventing ras-related tumors or diseases caused by other related CAAX box containing proteins, by blocking the prenylation of ras oncogene products or related CAAX box containing proteins by blocking the enzyme protein-prenyl transferase from catalyzing the transfer of the prenyl group from the prenyl pyrophosphate to the cysteine of the CAAX box.

8. Use of a protein-prenyl transferase inhibitor for the manufacture of a medicament for preventing prenylation of CAAX box containing proteins to inhibit the disease promoting effects of that protein in a mammalian species.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 9184

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	CELL vol. 62, 1990, pages 81 - 88; YUVAL REISS ET AL.: 'Inhibition of purified p21ras farnesyl:protein transferase by cys-AAX tetrapeptides' * abstract * * page 86 *	1-4,7,8	A61K31/66
Y	CANCER CELLS vol. 3, no. 9, 1991, pages 331 - 340; CHANNING J. DER ET AL.: 'Isoprenoid modification and plasma membrane association: critical factors for ras oncogenicity' * abstract * * page 337, left column * * page 338, right column *	1-4,7,8	
Y	CELL vol. 65, no. 1, 1991, pages 1 - 4; JACKSON B. GIBBS: 'Ras C-terminal processing enzymes-new drug targets?' * page 2, right column - page 4, left column *	1-4,7,8	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K
A	MOL.CELL.BIOL. vol. 10, no. 11, 1990, pages 5945 - 5949; ROSALIND KIM ET AL.: 'Prenylation of mammalian ras protein in xenopus oocytes' * page 5945, right column; figure 1 *	5,6	
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 31, no. 10, 1988, pages 1869 - 1871; SCOTT A. BILLER ET AL.: '(phosphinylmethyl)phosphonates as inhibitors of squalene synthetase' * the whole document *	5,6	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	18 DECEMBER 1992	TZSCHOPPE D. A.

EPO FORM 1503 03.82 (P0401)

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 356 866 (E.R.SQUIBB & SONS, INC.) 7 March 1990 * abstract *	5,6	
A	EP-A-0 418 814 (E.R.SQUIBB & SONS, INC.) 27 March 1991 * abstract *	6	
P,Y	EP-A-0 456 180 (E.R.SQUIBB & SONS, INC.) 13 November 1991 * abstract *	1-4,7,8	
P,X	BIOCHEM. BIOPHYS. RES. COMM. vol. 181, no. 2, 1991, pages 729 - 735; NAGARATNAM P. DAS ET AL.: 'Inhibition of farnesyl transferases from malignant and non-malignant cultured human lymphocytes by prenyl substrate analogs' *discussion * * abstract *	1-4,7,8	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

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Place of search	Date of completion of the search	Examiner
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